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EXAMINER	
WOODWARD, CHERIE M	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,467	SEBALD, WALTER	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 25-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-9, 11-23, and 25-29* is/are rejected.

7)☒ Claim(s) *3 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 17 October 2005 has been entered.

Applicant's Amendment of 4 April 2005, adding new claims 27-29 is acknowledged. The amendment dated 4 April 2005 has been entered into the record. After entry of the amendment, claims 1-23 and 25-29 are pending, as drawn to the elected invention of SEQ ID NO: 1. Claims 3 and 10 are withdrawn from examination as to a non-elected invention. Claims 1-2, 4-9, 11-23, and 25-29 are under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Objections/Rejections Withdrawn

2. Applicant's arguments, see Remarks, filed 17 October 2005, with respect to claims 1, 2, 4-7. 9, and 11-26 encompassing non-elected subject matter have been fully considered and are persuasive. The objection to claims 1, 2, 4-7. 9, and 11-26 as encompassing non-elected subject matter has been withdrawn.

3. Applicant's Arguments, see Remarks, filed 17 October 2005, with respect to claims 1, 2, 4-7, 9, and 11-26 under 35 U.S.C. 103 as being unpatentable over U.S. Application publication number 2001/0020086 (the '086 application, previously cited in the Office Actions of 29 September 2004 and 17 June 2005) in view of US Patent 5,652,332 (the '332 patent), previously have been considered but are moot in view of the new grounds of rejection.

4. Applicant's Arguments, see Remarks, filed 17 October 2005, with respect to the rejection of claims 24-26 under 35 U.S.C. 112, first paragraph, as lacking enablement (previously cited in the Office Actions of 29 September 2004 and 17 June 2005) have been fully considered, and are persuasive in light of Applicant's cancellation of claim 24 and amendments of claims 25-26 removing the recitation of therapeutic purpose.

Response to Arguments/Claim Rejections Maintained

Claim Rejections - 35 USC § 102

5. Applicant's Arguments, see Remarks, filed 17 October 2005, with respect to the rejection of claims 1, 2, 4-7, 9, and 11-23, and 25-26 under 35 U.S.C. 102 as being anticipated by U.S. Application publication number 2001/0020086 (the '086 application, previously cited in the Office Actions of 29 September 2004 and 17 June 2005) have been fully considered but they are not persuasive.

Applicant argues that the '086 application fails to anticipate amended claims 1 and 17 and claims dependent therefrom because the cited reference fails to teach every element of the currently claimed invention, as amended. Claim 1 has been amended to recite "a bone morphogenic protein (BMP) or a growth differentiation factor". Claim 17 has been amended to delete the reference to SEQ ID NO: 2, which was a non-elected invention. Specifically, Applicant argues that the sequence CRKRCN/CRKNRCN which is part of human lipoprotein lipase, is a protein that falls outside of the limitations of the claims, as amended. Additionally, Applicant asserts that the '086 application teaches the additions of heparin-binding domains to proteins that do not have a native heparin-binding domain, but that the instant claims the oligopeptides of SEQ ID NO: 1 are added to, inserted into, and/or substituted into polypeptides that contain heparin-binding domains, namely members of the BMP and GDF families.

The '086 application teaches as previously cited in the Office Actions of 29 September 2004 and 17 June 2005. Contrary to the assertions of Applicant's representative, the '086 application in fact recites the sequence CRKRCN in Table 1, at page 2. However, the Hata *et al.*, reference (cited within the '086 Table 1) recites the sequence as CRKNRCN, a heparin-binding domain of human lipoprotein lipase (LPL). Thus, the former Examiner correctly recited the sequence from the '086 application in the Final Office Action of 17 June 2005. Rather, it was the '086 Application that contained the typographical error in Table 1, as relied upon by the Examiner, and confirmed by the Hata *et al.*, reference, also cited therein.

Additionally, the '086 application teaches the addition of heparin-binding domains to <u>any</u> growth factor (paragraph 0011). Any growth factor would encompass the BMPs and GDF proteins claimed by Applicant.

The instant claims, as written, do not contain a limitation requiring that that the polypeptide variant of SEQ ID NO: 1 be added and/or inserted into a polypeptide containing a naturally occurring heparin-binding site. That limitation is only applicable to claim 1, subpart (iii), which is read in the

alternative. Because claim 1, subpart (iii) is immediately preceded by the phrase and/or, the claim can be read to encompass, for example, subparts (i) or (ii) or (iii); subparts (i) or (ii) and (iii); subparts (i) and (ii) or (iii); subparts (i) and (ii) and (iii). Thus, the claim can be read on the inclusion of subpart (iii) in the alternative, that the addition/insertion may occur in a polypeptide that does not naturally contain a heparin-binding site. The '086 application teaches the addition and insertion of heparin-binding domains in growth factors that contain naturally occurring heparin-binding domains as well as in growth factors that do not contain naturally occurring heparin-binding domains (see paragraph 0004).

Additionally, each of the subparts uses the language "comprising". Any addition and/or insertion, and/or substation of a naturally occurring amino acid sequence to any BMP or GDF protein would be contemplated by the claims, as written, so long as the oligopeptide comprises SEQ ID NO: 1, which can be as few as three amino acids in length and must contain at least two consecutive basic amino acids (see Remarks, filed 17 October 2005, page 13 of 21, last paragraph).

The rejection of claims 1, 2, 4-7, 9, and 11-26 under 35 U.S.C. 102 as being anticipated by U.S. Application publication number 2001/0020086 (the '086 application) is maintained for the reasons of record in the Office Actions of 29 September 2004 and 17 June 2005, and for the reasons stated herein.

Claim Rejections - 35 USC § 103

6. Applicant's Arguments, see Remarks, filed 17 October 2005, with respect to the rejection of claim 8 under 35 U.S.C. 103 as being unpatentable over U.S. Application publication number 2001/0020086 (the '086 application) in view of Linkhart *et al.*, (previously cited in the Office Actions of 29 September 2004 and 17 June 2005) have been fully considered but are not persuasive.

Applicant traverses the rejection stating that it may also be applied to amended claim 1 and claims dependent therefrom, including amended claim 8. Applicant argues that there was no motivation to combine the teachings of the '086 application and the Linkhart *et al.*, reference. Applicant argues that the heparin-binding domains discussed in the '086 application would be expected to increase the binding of a polypeptide to heparin, but that there is no teaching in the '086 application that the heparin-binding domains confer binding to bone in a site-specific manner.

The '086 application teaches heparin-binding growth factors non-covalently bound in gels and matrices (see paragraphs 0004, 0008, and 0009). The '086 application also teaches that careful selection of the enzymatic degradation site of the matrices can be accomplished by a stated means to permit sequestration of proteins and targeted release at specific sites of interest. The sequestration into the matrix occurs by the incorporation of heparin into the fibrin via the covalent immobilization of heparin-

binding peptides (see paragraph 0008). When the teachings of the '086 application are combined with the teachings of Linkhart *et al.*, it would be obvious to one of ordinary skill in the art to use the heparin-binding sequestration techniques taught by the '086 application to target BMPs and GDFs to the site of bone, as taught by Linkhart *et al.*

Additionally, the '086 application states that despite their relatively strong affinity for heparin, growth factors that contain heparin-binding domains dissociate from the matrix on a short time scale. Thus, adding heparin-binding sites to proteins that do not contain heparin-binding sites and adding additional heparin-binding sites to proteins that already contain heparin-binding sites are taught because a high excess of heparin-binding sites "is essential to ensure that the growth factors do not diffuse far before they bind to the matrix again" (paragraph 0013). Thus, the addition of heparin-binding sites in modified proteins and in matrices would cause the potent active growth factors to remain localized or be restricted in their diffusion.

The rejection of claim 8 under 35 U.S.C. 103 as being anticipated by U.S. Application publication number 2001/0020086 (the '086 application) in view of Linkhart *et al.*, is maintained for the reasons of record in the Office Actions of 29 September 2004 and 17 June 2005, and for the reasons stated herein.

Claim Rejections - 35 USC § 112, First Paragraph

Enablement

7. Applicant's Arguments, see Remarks, filed 17 October 2005, with respect to the rejection of claims 1, 2, 4-9, 11-23, and 26-26 under 35 U.S.C. 112, first paragraph, as lacking enablement (previously cited in the Office Actions of 29 September 2004 and 17 June 2005) have been fully considered but are not persuasive.

Applicant argues that SEQ ID NO: 1 requires at least two out of three amino acids to be basic amino acids. Applicant also argues that the claimed motif may consist of only 3 amino acids when X_3, X_5, and X_6 are no amino acid). Applicant states that the positively charged motif is complementary to negatively charged heparin or heparin-like substances. Applicant further argues that the features of the claimed heparin-binding motif need not, nor are they meant to, encompass each and every heparin-binding domain, such that there may exist heparin-binding motifs that fall outside the scope of SEQ ID NO: 1. Applicant additionally argues that the experiments needed to determine whether an oligopeptide encompassed by SEQ ID NO: 1 increases heparin-binding ability to a heterologus peptide requires anything more than routine experimentation. Finally, applicant argues that one skilled in the art would

recognize that the essential feature of the structural motif of SEQ ID NO: 1 are: (1) a specific charge distribution to 2 of 3 positively charged (basic) amino acids, (2) followed by 1 to 3 non-positively charged (non-basic) amino acids, (3) wherein the positively charged motif is complementary to the negatively charged heparin or heparin-like substances. Applicant's arguments are not persuasive.

As the previous examiner has stated, the claims encompass many more proteins, sequences, and motifs than Applicant has taught in the specification. Applicant has failed to teach all proteins that include a consensus sequence that comprises SEQ ID NO: 1. In this case, the species does not predict the genus, as the genus encompasses a vast number of proteins, such that any protein would be encompassed within the claims as long as the sequence comprised at least 2 to 3 basic amino acids followed by 1 to 3 non-basic amino acids. Applicant has not taught how to make and use every claimed variant.

General guidance is given regarding how to make and test variants of any protein. The scope of the patent protection sought by Applicant as defined by the claim fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. Certain positions in the sequences are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie *et al*, 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, Biochemistry 29:8509-8517; Ngo *et al.*, 1994, The Protein Folding Problem and Tertiary Structure Prediction, Merz et al., eds, Birkhauser, Boston, pp. 491-495).

However, Applicant has provided little or no guidance beyond the mere presentation of predicted sequence data (i.e. as long as the sequence comprised at least 2 to 3 basic amino acids followed by 1 to 3 non-basic amino acids) to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. by amino acid additions, insertions, or substitutions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if specific heparin-binding sites were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site

must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

The claims read on a polypeptide variant comprising SEQ ID NO: 1 that are characterized in a specified manner (see claim 1). Because the claimed variants comprise SEQ ID NO: 1, the numbers of potential proteins that may contain X_1, X_2, and X_4 are far greater than the 153 out of 8000 stated in Applicant's argument (see page 17 or 21, first full paragraph). If SEQ ID NO: 1 were limited to variants consisting of SEQ ID NO: 1, Applicant's statistics would be more in line with a reasonable amount of routine experimentation in order to determine whether specified peptides fulfill the requirements of SEQ ID NO: 1. However, as currently written, the number of proteins that contain a two basic amino acid stretch followed by one to three non-basic amino acids is simply too vast and would require undue experimentation to test all of the potential peptides comprising SEQ ID NO: 1.

Due to the large quantity of experimentation necessary to generate the numerous derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The rejection of claims 1, 2, 4-9, and 11-26 under 35 U.S.C. 112, first paragraph, as lacking enablement, is maintained for the reasons of record in the Office Actions of 29 September 2004 and 17 June 2005, and for the reasons stated herein.

8. Applicant's Arguments, see Remarks, filed 17 October 2005, with respect to the rejection of claim 7 under 35 U.S.C. 112, first paragraph, as lacking enablement (previously cited in the Office Actions of 29 September 2004 and 17 June 2005) have been fully considered but are not persuasive.

The claim recites a polypeptide variant of claim 1 characterized by alterations where the alteration shows at least 10% of the biological activity of the unaltered polypeptide and at least 90% homology to the unaltered peptide. Applicant argues that claims specifying variants of a polypeptide constrained by 90% homology and retention of some biological activity have been routinely granted by the PTO (see Remarks, p. 18 of 21). Applicant also argues that routine experimentation is required to make and use the polypeptide variants that satisfy the requirements for increased heparin-binding ability,

with at least 10% of the biological activity of, and at least 90% homology to, the respective unaltered BMP or GDF polypeptide.

The assertion that the disclosed SEQ ID NO: 1 has biological activities similar to known heparin-binding sites cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick *et al.* (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks *et al.* (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith *et al.* (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork *et al.* (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Additionally, Tischer *et al.* (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598;

see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polypeptide variants to make variants that retain at least 10% biological activity of the unaltered polypeptide and at least 90% homology to the unaltered polypeptide without resorting to undue experimentation to determine what the specific biological activities of the variant are.

Additionally, the specification does not teach the skilled artisan how to use the claimed polypeptide variants. For example, there is no evidence of tissue-specific expression patterns, such that the polypeptides encoding the claimed polypeptide variants could be used as a tissue-specific marker. Similarly, there is no disclosure of particular disease states correlating to an alteration in levels or forms of the claimed polypeptide variants such that the claimed polypolypeptide variants could be used as a diagnostic tool. Therefore, the skilled artisan is not provided with sufficient guidance to use the claimed polynucleotides for any purpose.

Due to the large quantity of experimentation necessary to determine an activity or property of the disclosed polypeptide variants such that it can be determined how to use the claimed polypeptide variants showing at least 10% of the biological activity of the unaltered peptide and at least 90% homology to the unaltered polypeptide, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The rejection of claim 7 under 35 U.S.C. 112, first paragraph, as lacking enablement, is maintained for the reasons of record in the Office Actions of 29 September 2004 and 17 June 2005, and for the reasons stated herein.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

9. Applicant's Arguments, see Remarks, filed 17 October 2005, with respect to the rejection of claims 1, 2, 4-9, 11-23, and 25 under 35 U.S.C. 112, first paragraph, as lacking written description (previously cited in the Office Actions of 29 September 2004 and 17 June 2005) have been fully considered but are not persuasive. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant argues that only two of three positively charged amino acid residues are required for the structural motif of SEQ ID NO: 1, with the third residue being and non-basic amino acid. Applicant also argues that Applicant is not claiming polypeptide variants modified to contain any heparin-binding domain, only those modified to contain at least one oligopeptide that satisfies the requirements of SEQ ID NO: 1. Further, Applicant argues that the claimed genus is not so limited in its structural requirements because there are restrictions on size, composition, and order of amino acids (see, Remarks at 20 of 21, first paragraph). This would be true, but for Applicant's use of the term comprising.

The claims read on a polypeptide variant with increased heparin-binding ability comprising SEQ ID NO: 1 that are characterized in a specified manner. As currently written, the claimed polypeptide variants are any that comprise a two basic amino acid stretch followed by one to three non-basic amino acids. Additionally, the claims, as written, do not contain a limitation requiring that that the polypeptide variant of SEQ ID NO: 1 be added and/or inserted into a polypeptide containing a naturally occurring heparin-binding site. That limitation is only applicable to claim 1 (and its dependent claims), subpart (iii), which is read in the alternative. Because claim 1, subpart (iii) is immediately preceded by the phrase and/or, the claim can be read to encompass, for example, subparts (i) or (ii) or (iii); subparts (i) or (ii) and (iii); subparts (i) and (ii) or (iii); subparts (i) and (ii) and (iii). Thus, the claim can be read on the inclusion of subpart (iii) in the alternative, such that the addition/insertion may occur in a polypeptide that does not naturally contain a heparin-binding site.

Additionally, each of the subparts uses the language "comprising". Any addition and/or insertion, and/or substation of a naturally occurring amino acid sequence to any BMP or GDF protein would be contemplated by the claims, as written, so long as the oligopeptide comprises SEQ ID NO: 1, which can be as few as three amino acids in length and must contain at least two consecutive basic amino acids (see Remarks, filed 17 October 2005, page 13 of 21, last paragraph).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., a therapeutic agent, a reference molecule, and a therapeutic index.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is a single species of the claimed genus that is disclosed within the scope of the claimed genus, *i.e.* polypeptide variants of SEQ ID NO: 1 with increased heparin-binding ability. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. The term "oligopeptide variant comprising [SEQ ID NO: 1] " reads on any

polypeptide variant comprising at least two basic amino acids followed by at least one non-basic amino acid. Applicant has not adequately described all possible polypeptide variants comprising SEQ ID NO: 1 for all known polypeptides in any species.

There is substantial variability among the species. In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a polypeptide variant with increased heparin-binding ability comprising at least two basic amino acids followed by at least one non-basic amino acid. One of skill in the art would not recognize from the disclosure that the Applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

The rejection of claims 1, 2, 4-9, and 11-25 under 35 U.S.C. 112, first paragraph, as lacking written description, is maintained for the reasons of record in the Office Actions of 29 September 2004 and 17 June 2005, and for the reasons stated herein.

New Claim Rejections- Necessitated by Amendment

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant uses the phrase "physiologically compatible additives" but fails to define the phrase in the specification or otherwise clarify what is meant by the term. A physiologically comparable additive could be saline or water.

Claim Rejections - 35 USC § 102

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. Claims 27 is rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Application publication number 2001/0020086 (the '086 application), as discussed *supra*. The '086 application teaches heparin-

binding growth factor fusion protein constructs, transformed vectors, plasmids, expression in bacterial systems, including E. coli (paragraph 0090).

Claim Rejections - 35 USC § 103

14. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

15. Claims 1, 2, 4-9, 11-23, and 25-28 under 35 U.S.C. 103 as being unpatentable over U.S. Application publication number 2001/0020086 (the '086 application, previously cited in the Office Actions of 29 September 2004 and 17 June 2005) in view of Ruppert *et al.*, Eur J. Biochem 1996 Apr 1; 237(1):295-302.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The '086 application teaches as previously cited in the Office Actions of 29 September 2004, 17 June 2005, and *supra*. The '086 application does not teach the process of producing a polypeptide variant using CHO cells.

Ruppert *et al.*, teach BMP-2 polypeptide variant EHBMP-2 proteins containing the heparin-binding sequence KKTQL (see age 296, column 2, third paragraph) (conforming to the limitations of SEQ ID NO: 1). Ruppert *et al.*, teach the construction of EHBMP-2 by substituting the normal N-terminal residues 1-12 of mature BMP-2 with a dummy sequence of comparable length and polarity but containing only two basic residues (see Figure 8, p. 300). The EHBMP-2 variant exhibits a 15-20 fold increased in specific activity compared with the natural BMP-2 (p. 298, column 2, last paragraph). Ruppert *et al.*, also teach the importance of three-dimensional structure of BMP-2 and the conformation adopted by the N-terminal heparin-binding sites (p. 300, column 1, second paragraph). Ruppert *et al.*, teach the importance of the occurrence of multiple basic triplets (i.e. three consecutive basic residues) in the heparin-binding sequence of BMP-2, as well as the longer N-terminals of BMP-3, 5, 6, 7 and 8 and

also in GDF-5 that is also conserved in Drosophila and X. laevis with two conservative substitutions (p. 300, column 1, last paragraph, to column 2, first paragraph).

It would have been obvious to a person of ordinary skill in the art at the time the invention was filed to make polypeptide variants with increased heparin-binding ability by combining the teachings of the '086 application and Ruppert *et al.* Ruppert *et al.*, show that mutating the N-terminal region of BMP-2 increases the specific activity of heparin-binding in the variant protein (p. 298, column 2, last paragraph). One of ordinary skill in the art would have reasonably expected success because both the '086 application and Ruppert *et al.*, successfully produced growth factor variants containing cysteine knots, in E. coli.

Additionally, one of ordinary skill in the art would have been motivated to produce the heparin-binding polypeptide variants in CHO cells (as taught by Ruppert *et al.*, p. 297, column 2, first paragraph) in order to determine the effects of post-translational modifications on the variants (for example, to compare the effects of the absence of N-glycosylation) that could effect physical and functional properties of the modified polypeptide variants. A person of ordinary skill would have reasonably expected success because both the '086 application and Ruppert *et al* successfully teach the process of generating the heparin-binding polypeptide variants in E. coli.

16. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over the '086 application in view of Meddahi *et al.*, Path Res. Pract. 190, 923-928 (1994). Claim 29 recites a pharmaceutical composition as recited in claim 23, further comprising physiologically compatible additives.

The '086 application teaches as previously cited in the Office Actions of 29 September 2004 and 17 June 2005. Pharmaceutical compositions are taught at paragraph 0014. Meddahi *et al.*, teach heparin binding growth factors and pharmaceutical compositions of growth factors as wound healing agents (see p. 923, last paragraph). Meddahi *et al.*, teach heparin as a stabilizing and protective agent (p. 924, column 2, third paragraph.) Additionally, Meddahi *et al.*, teach a heparin-binding growth factor-like composition with or without a saline buffer (p. 925, column 1, paragraphs 4 and 9). It would have been obvious to a person of ordinary skill in the art at the time the invention was filed to add a physiologically compatible additive to the pharmaceutical composition, such as a saline buffer, and would have reasonably expected success because it is well known in the art that saline buffers are physiologically compatible additives.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly

owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CMW

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